Oxidative Stress and Ischemic Heart Disease (IHD) and Respiratory Disease (COPD) Mortality in the Golestan Cohort of Tobacco Users

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Abstract

Background: Biomarkers predictive of disease could improve our understanding of new tobacco product health risks. Oxidative stress from exposure to tobacco smoke has a role in the pathogenetic process leading to chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD). The urinary metabolite 8-isoprostane is a biomarker of oxidative stress.
Methods: We conducted a nested case-cohort analysis within the prospective Golestan Cohort Study (GCS) to estimate the relationship between 8-isoprostane concentration and mortality due to IHD and COPD. The GCS enrolled 50,045 Iranian adults ages 40-75 years between 2004-2008 and collected tobacco use data and urine specimens. Mortality was assessed by active follow-up through 2017. At baseline, we selected a stratified random sample of disease-free participants from age (+/- 55 years), sex (male/female), region (urban/rural) and smoking status (yes/no) groups. We measured 8-isoprostane concentration in baseline spot urine samples. We estimated the risk of IHD and COPD mortality by tertiles of creatinine-corrected 8-isoprostane among current cigarette smokers using Cox proportional hazards regression adjusting for socioeconomic status, physical activity, body mass index, opiate use, smoking intensity and smoking duration. The IHD model additionally adjusted for diabetes and hypertension.
Results: We included 177 cases, 166 noncases in the IHD analysis and 60 cases and 173 noncases in the COPD analysis. The risk of IHD did not differ by 8-isoprostane tertile (T1: OR=1.0, T2: OR=0.7 (95% CI 0.3, 1.6), T3: OR= 1.1 (95% CI 0.5, 2.6). In contrast, the risk of COPD was significantly greater in T2 (OR: 5.7, 95% CI 1.3, 25.2), and greater in T3 (OR: 4.8, 95% CI 0.95, 24.6) compared to T1.
Conclusion: We demonstrate that a baseline measure of an oxidative stress biomarker among smokers is associated with greater mortality risk of COPD, but not IHD, over an average of ten years of follow-up. This is one of the first investigations to link a biomarker measure and smoking-related disease outcomes and informs potential use of biomarkers to predict future disease risk.

Introduction

Background

- Smoking is causally related to both ischemic heart disease (IHD) and respiratory diseases including COPD through inflammatory pathways leading to oxidative stress; oxidative stress plays a role in the etiology of both disease outcomes
- Urinary concentration of 8-isoprostane is a stable long-term biomarker of oxidative stress
- The Golestan Cohort Study (GCS) located in a northeastern province of Iran includes demographic information, tobacco use reporting and baseline biospecimen collection in which biomarkers were measured
- The study enrolled 50,045 Iranian adults ages 40-75 years old
- Participants lived in both urban (20%) and rural locations (80%) within the province
- The GCS enrollment period was 2004-2008; participants were actively followed for mortality outcomes through 2017
- We used a nested case-cohort study design to analyze these data

Aims

- Compare geometric mean concentration of 8-isoprostane by mortality outcome (IHD and COPD) among current smokers
- Estimate the mortality risk of IHD and COPD by 8-isoprostane tertile among current and noncurrent smokers adjusting for potentially confounding variables
- Perform Sub-Group Analyses by enrollment year, by duration/intensity smoking, by opiate use, and by obesity

Materials and Methods

- We identified all IHD and COPD deaths from the total GCS population who also provided a urine sample at baseline, and we selected a selected a stratified random sample of cancer-free participants from the baseline total cohort (strata: age, sex, region and smoking status).
- Sampling strategy allowed us to make inference to the overall cohort.
- Created tertiles based on the 8-isoprostane biomarker distribution among controls
- Outcomes ascertained through physician medical record review and included respiratory deaths (COPD, asthma, and pulmonary embolism, other) and ischemic heart disease
- Adjusted for sex, residence, education, waist circumference, hip circumference, diabetes, hypertension, duration of cigarette smoking, cigarettes per day, duration of opium use, opium units per day (nokhod) and log-transformed creatinine.
- Current smoker includes cigarette smoker, many also include current or former users of other tobacco products.
- Noncurrent smoker includes never smokers, former cigarette smokers or current or former users of other tobacco products
- Calculated geometric mean and estimated adjusted hazard ratio using Cox PH regression accounting for stratified random sampling approach modified for nested case-cohort design (Taylor linearization methods)
- Tested for heterogeneity (Paternoster et al 2-sided Z-test for equality of coefficients 1998)

Results

- The analytic sample included 576 GCS participants including 177 heart disease deaths and 60 respiratory disease deaths compared to 166 and 173 noncases, respectively
- Among current smokers, IHD or COPD deaths were more likely to be older, have less education attainment, report diabetes and hypertension and have long smoking duration and opium use.
- Among current smokers, the geometric mean concentration of 8-isoprostane was similar between IHD cases and controls but was greater among cases of respiratory disease deaths than noncases (1294 pg/mg creatinine v. 1064 pg/mg creatinine) (Table 1)

	Current Smokers Cases		Current Smoker Noncases	
	N	Geometric Mean (SE) pg/mg	N	Geometric Mean (SE) pg/mg
IHD	177	1064.8 (37.1)	166	1062.6 (62.8)
COPD	60	1294.1 (77.7)	173	1064.0 (61.3)

Table 1. Geometric mean concentration of 8-isoprostane by heart disease and respiratory disease mortality status among current smokers

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Results (continued)

- We did not observe a different IHD mortality risk among smokers controlling for sex, residence, education, waist circumference, hip circumference, diabetes, hypertension, duration of cigarette smoking, cigarettes per day, opium units per day (nokhod) and log-transformed creatinine. (Table 2)
- The addition of wealth score, history of IHD or stroke did not alter results.
- We also performed this analysis among noncurrent smokers and did not observe different risk estimates

	Heart Disease Hazard Ratio	95% CI	p-value
8-Isoprostane (#cases/controls)			
Ref (70/59)	1.0		
Tertile 2 (51/60)	0.73	(0.33, 1.6)	0.45
Tertile 3 (56/47)	1.11	(0.47, 2.6)	0.82

Table 2. Heart Disease Mortality Risk of 8-isoprostane among current smokers

- However, we observed an approximate 5-fold increased mortality risk among those in the upper tertiles of 8-isoprostane compared to the lowest tertile among current smokers adjusting for sex, residence, education, waist and hip circumference, duration of cigarette smoking (years), cigarettes per day, duration of opium use (years), units of opium per day (nokhods), and log-transformed creatinine. (Table 3)
- The upper tertile was also elevated, however not statistically significantly so, likely due to the small number of COPD cases (n=8).
- We observed no association among noncurrent smokers

	Respiratory Disease Hazard Ratio	95% CI	P-value
8-isoprostane (#cases/controls)			
Ref (26/63)	1.0		
Tertile 2 (26/62)	5.7	(1.3, 25.2)	0.02
Tertile 3 (8/48)	4.8	(0.95, 24.6)	0.06

Table 3. Respiratory Disease Mortality Risk by 8-isoprostane among current smokers

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- We observed increased risk of death from heart disease among those who are in the normal BMI range and no association among those who are obese. (Table 4)
- However, our results did not differ by enrollment year, smoking intensity, opiate use among either IHD or respiratory disease.

Table 4. Stratified analysis of Heart Disease Mortality by Obesity Status

BMI <25			BMI>25		
8-isoprostane Tertile (#cases/controls)	HR	95% CI	8-isoprostane Tertile (#cases/controls)	HR	95% CI
Ref (39/44)	1.0		Ref (31/15)	1.0	
Tertile 2 (34/37)	2.07	0.72, 5.9	T2 (17/23)	0.17	0.02, 1.15
Tertile 3 (35/30)	1.95	0.60, 6.28	T3 (21/17)	0.27	0.05, 1.5

Discussion

- Lack of an association with IHD mortality may be due to heterogeneous outcome, small sample size may have weakened associations; results differ from other studies (Xuan 2018; Yuan 2018; Vasalle 2003)
- The 10-year follow-up may be inadequate to discern difference in IHD mortality risk in a relatively young cohort (average age cases among smokers is 57 years)
- Regarding the observation of different HR by obesity status in the relation between the biomarker and IHD mortality, another study has reported a similar findings and they suggest that once a person has a strong risk factor for heart disease, the addition of 8-isoprostane to the model has low influence on the effect size
- Strong association with respiratory disease/COPD mortality among smokers may be due to strong biological factors of inflammatory/oxidative stress in COPD development and progression; all respiratory conditions we modeled (COPD, respiratory disease, asthma) involve inflammatory responses
- Strengths of study include use of specific 8-isoprostane isomer (v. summed F2-isoprostane), 10-years follow-up time, physician confirmed death, adjustment for important risk factors
- Limitations include no information on the recency of smoking to biospecimen provision, baseline exposure assessment only possibly leading to exposure misclassification

Conclusions

- Results demonstrate baseline oxidative stress biomarker 8-isoprostane concentration is associated with mortality from respiratory disease 10+ years later
- Unique addition to literature as our method allows isolation of 8-isoprostane (and not the summation of F2-isoprostane isomers)
- Modeling IHD/CHD mortality requires knowledge of many heart disease and stroke risk factors and ample sample size to investigate in robust statistical model among current smokers only
- Biomarker results such as these can inform potential health effects of new tobacco products and tobacco use behaviors (dual and poly-use) that present similar chemical exposures